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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,259	07/09/2004	Shunichi Shiozawa	61646 (70904)	7532

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
11/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,259	SHIOZAWA ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 9/11/2007.

This is action is directed to amended claim 4 of the instant specification.

This action contains new ground of rejection and thus is non-final,

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/11/2007 has been entered.

37 CFR1.132 declaration

2. The declaration under 37 CFR 1.132 filed 9/11/2007 is insufficient to overcome the rejection of claim 4 based upon enablement as set forth in the last Office action because: see discussion below.

Sequence compliance

3. The application fails to comply with CFR 1.821(d), which states:

(d)Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier,

preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, Figure 3, contains a nucleic acid sequence. Applicant is required to check the rest of the disclosure for any other nucleic acid or protein sequences and list them in a sequence listing and identify them with a proper SEQ ID NO.

The specification must be amended to bring it into sequence compliance. **A response to this office action will be held non-compliant if the specification has not been amended to make it sequence compliant.**

Drawings

4. The drawings are objected to because figure 3 contains nucleic acid sequences not properly identified by SEQ ID NO. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are

not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance. Alternatively the specification can be amended and the nucleic acid sequences in the figure may be identified in the description of the drawings.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claim 4 encompasses a method of evaluating the possibility of onset or onset of rheumatoid arthritis (RA), by detecting the presence or absence of a gene homozygously expressing a protein comprising the amino acid sequence as show in SEQ ID NO 1. Thus the claims broadly encompass evaluating the onset of RA by the detection of presence or absence of "any" nucleic acid that would result in a protein comprising the amino acid sequences of SEQ ID NO 1, as a single gene will homozygously express the protein which it encodes.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches the insertion of GGT at positions 805-807 resulting in a glycine being inserted into amino acid position 269 of SEQ ID NO.1 (see page 25, 1st full paragraph). The specification further teaches this insertion is depicted in SEQ ID NO. 2 (see page 25, line 10). The specification teaches a 3 base deletion (see page 10, line 11).

The specification teaches the homozygous or heterozygous deletion of "GGT" in SEQ ID NO. 2 occurs in 98.5% of subjects with familial history RA, diagnosed with RA (see Figure 4). The specification further teaches 100% subjects with familial history RA, not diagnosed with RA, were homozygous or heterozygous for deletion of "GGT" in

SEQ ID 2 (see figure 4). The specification further teaches 98.2% of subjects with sporadic RA were homozygous or heterozygous for the "GGT" deletion. While 100% of the subjects related to those diagnosed with sporadic arthritis have the homozygous or heterozygous "GGT" deletion.

The specification further teaches the patients that homozygously lack the "GGT" deletion (that have GGT at position 805-807) have RA: familial RA (1.5%) and sporadic RA (1.8%). The specification appears to teach patients that homozygously lack the "GGT" deletion (that have GGT at position 805-807) were found only with RA, but the homozygous or heterozygous "GGT" deletion was found both in subject with RA and those without RA.

The specification teaches of 1410 alleles examined, 1296 were not SEQ ID NO1 and 114 were SEQ ID NO1. This suggests that SEQ ID NO 1 is an underrepresented allele in the population studied.

However, the claims are drawn to detecting the presence or absence of nt805Homo. Thus the claims broadly encompass the absence of nt805 HOMO being predictive of the possibility of RA, however the specification teaches in figure 4 that of 705 total subjects examined, there were 294 with RA and of the 294 with RA only 5 were homozygous for the presence of SEQ ID NO 1. Thus it appears that the absence of detecting a gene that encodes SEQ ID NO1 is not predictably associated with the onset or possibility of onset of RA.

The state of prior art and the predictability or unpredictability of the art:

The art teaches genetic variations and associations are often irreproducible.

Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed the skilled artisan would first have to determine if the presence or absence of a gene homozygously coding for a protein comprising the amino acids of SEQ ID No 1 is predictably associated with RA. As a gene homozygously expresses the protein which it encodes, the claim merely requires the presence of SEQ ID NO 1.

The claim broadly recites evaluating the onset or onset possibility of RA, but does not state the relationship between the step of detecting the presence or absence of a gene encoding SEQ ID NO: 1 and the step of evaluating. As the claims does not require a step of correlating the presence or absence of SEQ ID NO 1 with RA the skilled artisan would further have to determine if the presence of absence of SEQ ID NO1 is associated with an increased or decreased possibility of RA. It would be unpredictable to associate the detection of presence of SEQ ID NO 1 with RA as the specification clearly teaches in Figure 4 that SEQ ID NO 1 is found in 109 subjects (totaling 114 alleles), with 35% of the patients being disease free. Further the absence of SEQ ID No 1 is found in 596 subjects of which 223 did have RA. It is clear without statistical analysis the presence or absence of SEQ ID NO1, by itself is not indicative of increased or decreased onset of RA. Further the low frequency of SEQ ID No 1 allele suggests that it is a very allele and thus the presence may not be indicative of anything.

Further it would be unpredictable to associate the homozygous absence of a gene encoding a protein with the sequence of SEQ ID NO 1 with an increased possibility of onset of RA, as 700 of the 705 subjects examined were not homozygous for the presence of SEQ ID NO 1. Of the 700 subjects that were not homozygous for

SEQ ID NO 1, almost half (344) do have RA. Thus as half of the subjects without SEQ ID No 1 did have RA, it would be unpredictable to same the homozygous absence of SEQ ID No 1 is associated with either an increased or decreased chance of onset of RA.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response filed on 9/11/2007 asserts the specification and information of the 1.132 declaration would allow one of ordinary skill in the art to "evaluate the onset or onset possibility of rheumatoid arthritis in a human subject by detecting the homozygous presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 (as described in the present application) in the subject, because the presence of the homozygous insertion mutation (the 3-base insertion at positions 805 to 807 in the nucleic acid sequence coding for Angiopoietin-1) is associated with rheumatoid arthritis, as described in the present application and in the experiment described herein." This argument has been thoroughly reviewed but is not found persuasive because the claim as described in the rejection the absence or presence of homozygous SEQ ID NO 1 is not predictably associated with RA.

Further the claim does not require the homozygous presence or absence of SEQ ID NO 1, but "a gene homozygously coding a protein comprising the amino acid sequences shown in SEQ ID NO 1." Thus the arguments to the homozygous presence of a gene coding SEQ ID NO 1 are not commensurate in scope with the claimed invention.

As for the 37 CFR 1.132 declaration, it is noted first that the declaration is from the applicant and merely describes an assay for detecting a region of SEQ ID NO 1. The presented table examines 200 subjects, of which 48 are homozygous for the insertion or presence of SEQ ID NO 1. Of the 48 homozygous for SEQ ID No 1, 15

(almost a third) do not have RA. It thus suggests that the homozygous presence of SEQ ID NO 1 is not indicative of sporadic RA, as a third of patients homozygous for SEQ ID NO 1 do not have RA. Further 152 subjects were not homozygous for SEQ ID NO1 and 82 of the subjects had RA, thus the lack of homozygous SEQ ID NO 1 is not indicative decreased chances of RA.

The 1.132 declaration asserts there is a statistically significant trend for the insertion (SEQ ID NO 1 homozygous) (p=0.07), but does not teach if the trend is relative to all subjects, control subjects, RA patients with homozygous deletion or heterozygous deletion.

Further the comparison of the data from the specification and declaration suggest two different populations were studied suggesting the homozygous presence or absence of SEQ ID NO 1 is not predictably associated with RA. Specifically the data of the specification teaches SEQ ID NO 1 was homozygous in approximately 1% of 705 subjects examined, while the declaration teaches 17.6% of controls and 28.7% of sporadic RA patients were homozygous. This data appears to suggest that two quite different populations were studied, which leads one to question what the two populations are and if the results are predictable across all populations as claimed.

Thus the Enablement rejection has been modified and maintained.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in that it recites, "a gene homozygously coding." It is unclear how a gene homozygously codes for anything. A cell or a subject may be homozygous for a gene, but a gene cannot be homozygous for coding a protein. The claim should be amended to recite, "the homozygous presence of a gene encoding the sequence consisting of SEQ ID NO 1."

Claim 4 is further indefinite in that it does not recite a step suggesting whether the homozygous presence or absence of SEQ ID No 1 results in an increased or decreased possibility of onset of RA.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claim 4 is rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Hillman et al (US Patent publication 2002/0123054, published 9/5/2002).

The MPEP 2111 teaches:

> During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." >The Federal Circuit's en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) expressly recognized that the USPTO employs the "broadest reasonable interpretation".

Claim 4 is broadly drawn to a method of evaluating onset or possibility of onset of RA by the detection of the presence or absence of a gene encoding SEQ ID NO 1. The recitation of "homozygously coding" makes the claim indefinite as a gene encodes a protein, but is not homozygous. The claim thus broadly encompasses detecting the presence of SEQ ID NO 1 and evaluating the possibility of RA. This rejection is based on the claim does not require an actual step of evaluating the onset or possibility of onset based on the presence of SEQ ID NO 1.

Hillman et al teaches a method of diagnosing rheumatoid arthritis by the use of fragments of instant SEQ ID NO 2, which Hillman identifies as angiopoeitin and correspond to the amino acid sequence of SEQ ID NO 1(see paragraph 0089). Hillman et al thus teach a method of comprising the step of detecting the presence or absence of SEQ ID NO 1 and the step of evaluating the onset of RA.

11. Claim 4 is rejected under 35 U.S.C. 102(a) as being anticipated by Shiozawa et al (Nippon Rinsho (2002) volume 60, pages 2269-2275)(translation pages 1-19).

Claim 4 is broadly drawn to a method of evaluating onset or possibility of onset of RA by the detection of the presence or absence of a gene encoding SEQ ID NO 1. The

recitation of "homozygously coding" makes the claim indefinite as a gene encodes a protein, but is not homozygous. The claim thus broadly encompasses detecting the presence of SEQ ID NO 1 and evaluating the possibility of RA. This rejection is based on the claim does not require an actual step of evaluating the onset or possibility of onset based on the presence of SEQ ID NO 1.

Shiozawa et al teaches on page 15 of the RA2 gene (angiopoietin-1) was found with the gly 269 insertion (SEQ ID NO 1) in 83/335 of RA patients, while in only 30 of 383 control patients. Shiozawa et al thus teaches a method of detecting the presence or absence of SEQ ID NO 1 and evaluating the onset of RA.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Carla Myers/
Primary Examiner, Art Unit 1634